

NIH COMMON FUND HIGH-RISK HIGH-REWARD RESEARCH SYMPOSIUM

December 15 – 17, 2014

SPEAKER ABSTRACTS – DAY 2 (DEC. 16, 2014)

The Transposon Storm Hypothesis: Collateral Damage in the Brain

Awardee: Josh Dubnau

Award: Transformative Research Award

Awardee Institution: Cold Spring Harbor Laboratory

Retrotransposons are inherited virus like repetitive elements that are capable of replicating and re-inserting into *de novo* locations within the genome. As a whole, retrotransposon sequences contribute a vast fraction of the genome, up to 40% in humans. To date, retrotransposition has been largely studied in germline where new insertions produce heritable genetic variants. In fact, the germline is the main battlefield of an evolutionary conflict between our genomes and retrotransposons. Plants and animals have evolved elaborate and effective mechanisms to silence retrotransposons, and they are largely effective. But transposons also are capable of mobilizing in somatic tissue. An emerging literature establishes that some retrotransposons are NORMALLY active at a low level in neurons during development. We have demonstrated, however, that in *Drosophila* the silencing mechanisms begin to falter with advancing age and collapse in genetic models of amyotrophic lateral sclerosis (ALS). This leads to accumulation of *de novo* mutations in neurons. We also have shown that genetically activating LINE-like and gypsy transposons results in accelerated effects of aging on neurophysiological decline. This leads to rapid age-dependent memory impairment, defects in locomotion, and to shortened lifespan. We also have found signatures of this transposon storm at the expression level in deep sequencing datasets from human subjects and in rodent models of ALS. Our findings have implications for the mechanisms of neurodegeneration seen in ALS and frontotemporal dementia.